REMARKS

Receipt of the Office Action of March 10, 2004 is acknowledged. Reconsideration of Claims 1-16 is respectfully requested in view of the above referred to amendments and the following argument. Favorable consideration of new Claim 17 is also requested.

A. Section 102 Rejection

Claims 1, 2 and 4 were again rejected as anticipated by the Plowman et al reference (Lancet). Claim 2 has been amended to identify dimesna (disodium 2,2'-dithiobis ethane sulfonate) as a preferred agent, and is not anticipated by Plowman.

Claim 1 is also not anticipated by Plowman. In this Office Action the only comments the Examiner makes regarding the teachings of the Lancet (Plowman) reference are that "mesna exhibits radioprotective properties," and that "A laboratory setting, in which mice are utilized, reasonably serves as an appropriate model for humans."

The Examiner also cites as a reference the 48th edition of Facts and Comparisons as showing the recommended IV dose of mesna to be 0.24 g/m^2, presumably to create an inference that an effective amount of mesna is somehow taught by the Lancet reference. However, the two references are contradictory as to what constitutes an "effective" amount of mesna. Plowman's "effective" dose is nearly 70 times greater than the dose recommended for IV mesna. The reference to Facts and Comparisons is further conclusive evidence that Plowman does not anticipate Claims 1, 2 and 4.

As previously argued, to anticipate a claim, a single reference must teach every element of the claim. MPEP 2131. There can be no doubt that Plowman utterly fails this requirement. As also argued in the Applicant's response to the Office Action of November 26, 2003, a dose of 400 mg/kg of mesna (30 grams of mesna in an average 75 kilogram human- the amount taught by Plowman to afford "effective" radioprotection) would be fatal (i.e., ineffective) to a human being. Facts and Comparisons (and also the USPDI and AHFS) actually confirms Applicant's arguments from the above response, by verifying that the effective dose of mesna (when used as a chemoprotectant) is about 1/70 of the amount disclosed to be administered by Plowman. The average human being has a body surface area of about 1.8 m^2, making the recommended dose of mesna to be about 0.42 grams. Doses of mesna above 1 gram (about 3% of the Plowman dose) have been observed to cause serious adverse effects in humans.

Plowman does not teach an effective dose of mesna in human beings, not for radioprotection or any other use. It therefore is not a proper anticipatory reference here.

B. Section 103 Rejection of Claims 1-4

Claims 1-4 were again rejected as obvious over van den Broeke, et al. Applicant reiterates the arguments advanced in the previously filed response, that the Examiner has incorrectly applied the limited teachings of the van den Broeke reference, and it is again respectfully submitted that no *prima facie* case of obviousness has been presented.

Van den Broeke teaches nothing that would motivate any person skilled in the art to administer mesna as a treatment for exposure to ionizing radiation. In addition to the arguments advanced previously, Applicant respectfully points out that even if van den Broeke

could be read to suggest radioprotective properties of mesna, those properties as taught by van den Broeke apply to Ultraviolet (UV) radiation only. Ultraviolet radiation is non-ionizing radiation, and falls into the same category as infrared, microwave and visible light radiation. Non-ionizing radiation, as its name suggests, does not cause ionization of the body's tissues nor does it cause systemic organ failure(s) as described in the present specification. UV radiation, as well as hypothetical treatments for UV exposure, is fundamentally and scientifically different than ionizing radiation. These differences are well known in the scientific and health care communities and are also clearly defined by the United States government. http://www.osha.gov/SLTC/radiation_nonionizing/. In conclusion, van den Broeke, et al fails even the most basic test for obviousness.

Section 112 Rejections

Claims 1-16 were also rejected under 35 U.S.C. 112, first paragraph. The Examiner alleges two grounds for this rejection, and these will be argued separately.

The Written Description is Adequate Pursuant Section 112

With regard to the Section 112 rejection dealing with sulfur-containing amino acids, Applicant must point out that this portion of the Claims was originally presented with the subject application at the time of filing, and the Examiner, through the course of three previous Office Actions, never once entered this rejection. MPEP 2163.03 provides strong support for withdrawal of the written description rejection.

"While a question as to whether a specification provides an adequate written description may arise in the context of an original claim which is not described sufficiently, there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). Consequently, rejection of an original claim for lack of written description should be rare." MPEP 2163.03 (2003). (Emphasis added)

None of the Claims of this application has ever been amended to add the sulfur-containing amino acid moiety as part of the genus of compounds useful in practicing the method of this invention. Given the prior history of this application, the Examiner had apparently concluded that the written description requirement had been satisfied as to this moiety.

The lack of a previous written description rejection is telling. Claims 1-16 recite a method of treatment, and the rejected part of the claims is but a species of a larger genus of compounds stated by Applicant to be useful in practicing the method. The various species that fit within the genus of formula I compounds is well defined. At page 9 of the specification, lines 8-10, Applicant specifically describes compounds of this species (cysteine, homocysteine and glutathione), which make clear to anyone skilled in the medical and pharmaceutical art fields what compounds are to be administered.

Further, the Examiner provides no evidence that the description is lacking- only the unsubstantiated speculation that "the present level of skill in the radiology art is immature with respect to radioprotection and would reasonably require a more detailed written description directed to the preparation and administration of compounds of instant formula I wherein a sulfur-containing amino acid is present." Not only is that conclusion unsupported by any evidence, the description teaches a skilled radiologist methods (oral and parenteral/IV) of administration of the formula I compounds as a genus. A radiologist has absolutely no need

for guidance in chemical synthesis of particular compounds, nor would any medical person skilled in the administration of such agents require such guidance.

In conclusion, the written description is adequate, as the Examiner had apparently concluded through all of the first three Office Actions issued with regard to the subject application. In any event, Claims 2 and 16 cannot be included in this rejection as they do not recite a sulfur-containing amino acid as part of the formula I compounds.

The Specification Is Enabling

The above arguments as they relate to adequate written description are reiterated here. The specification has not undergone any substantive modifications since the original filing, with only Claim 1 having been amended to refer to the treatment of human patients; the Examiner has heretofore previously found that the subject specification was both adequate and enabling. MPEP 706 states-

"After the application has been read and the claimed invention understood, a prior art search for the claimed invention is made. With the results of the prior art search, including any references provided by the applicant, the patent application should be reviewed and analyzed in conjunction with the state of the prior art to determine whether the claims define a useful, novel, nonobvious, and enabled invention that has been clearly described in the specification. The goal of examination is to clearly articulate any rejection early in the prosecution process so that the applicant has the opportunity to provide evidence of patentability and otherwise reply completely at the earliest opportunity." (emphasis added)

In attempting to justify the enablement rejection, the Examiner relies on several incorrect and/or otherwise irrelevant statements, and provides no factual evidence that could even begin to form a *prima facie* case of lack of enablement. One such statement is found at page 5 of the Office Action, "The specification provides no support specifically directed to

treatments wherein an outcome following the administration of such compounds shows any results whatsoever."

There is no support for the apparent conclusion of the Examiner that results must be disclosed in a specification to support enablement. Enablement does not require that the disclosure contain working examples, much less disclosure of any "results" of experiments. MPEP 2164.02. This finding is in line with numerous previous holdings of the Federal Circuit, (and, pre-1982, the CCPA) which held that the claimed invention need not have been reduced to practice prior to filing. *In re Borkowski*, 164 USPQ 642 (CCPA 1970).

Applicant notes the Examiner's citation to *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), and submits that the holdings of the Federal Circuit in *Wands* support the conclusion that the subject specification is clearly enabled.

The Court in *Wands* reversed the PTO finding of non-enablement and held that the disclosure (which related to a method of detecting Hepatitis B surface antigens) was sufficiently enabling after a determination that one skilled in the art would not need to perform undue experimentation to use the invention. As correctly noted by the Examiner, the Federal Circuit set forth an eight-point test for determining enablement. The errors and/or lack of findings by the Examiner will be argued as to each of the eight factors.

1. Breadth of the Claims- The Examiner's perfunctory conclusion, "The claims are very broad and inclusive of any parameter of ionizing radiation and radiation therapy" fails to objectively analyze the scope of any of the claims.

First, as the Examiner points out in this and other sections of the Office Action, the claims relate to methods of treatment for radiation exposure, or to methods for prophylactically treating a patient about to undergo radiation therapy.

Second, not all of the claims are of broad scope, particularly the dependent claims that limit the method to certain modes of administration and/or to certain compounds within the scope of the genus identified in the independent claims 1 and 5.

Apparently, the Examiner has drawn the "very broad" and "inclusive of any parameter" conclusions on the many different physiological manifestations that can result from exposure to ionizing radiation. Respectfully, the Examiner's conclusions are erroneous. Such conclusions are akin to labeling any method of treatment claim "very broad" when there are a number of physiological manifestations associated with an otherwise relatively simple disease or condition.

2. The Nature of the Invention- The Examiner is correct, at least in a broad sense, as to the nature of the invention.

3. State of the Prior Art- The Examiner made no statement whatsoever as to this factor.

4. Level of One of Ordinary Skill- The Examiner's conclusions regarding relative skill are incorrect. The claimed method requires the administration of a pharmaceutical compound. As such, the level of skill necessarily expands to those having expertise in the field of medicinal chemistry. Radiology experts do not generally possess expertise in the pharmaceutical arts.

5. Level of Predictability in the Art- Here, the Examiner again confuses the issue of which art field is relevant. Radiology is not the field this invention is directed to. The invention relates to a method of treating a condition that radiologists have knowledge, but the inventive method as claimed relates to the administration of medicinal compounds, and the appropriate art field to consider are those with advanced degrees (Ph.D and M.D.) and

expertise in medicinal chemistry. This invention is not directed toward M.D. radiologists or technicians, who often possess limited knowledge of medicinal chemistry.

The Examiner's conclusion that this art field is "highly unpredictable and unreliable with respect to conclusions drawn from laboratory data extrapolated to clinical efficiency" is highly contradictory to the Examiner's position in formulating an obviousness rejection of these same claims! The Examiner at page 2 of the current Office Action stated, "A laboratory setting in which mice are utilized, reasonably serves as an appropriate model for humans." The Examiner cannot have it both ways, claiming the art is predictable for purposes of formulating obviousness rejections, then flipping 180° and stating the art is unpredictable in an attempt to justify an enablement rejection.

6. Amount of Direction Provided By the Inventor; and 7. Existence of Working Examples- The Examiner ignores the amount of guidance provided in the specification, and concentrates only on the absence of specific examples.

Applicant submits that the amount of direction and guidance provided in the subject specification is considerable, and more than adequate to satisfy the enablement requirements of Section 112. As stated in MPEP 2164.01(b), "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 USC 112 is satisfied, *In re Fisher*, 166 USPQ 18 (CCPA 1970).

With regard to the formula I compounds that are disclosed as useful in the practice of the method, Applicant has identified numerous species that are encompassed within the scope of the broader formula I genus- mesna, dimesna, phosphonate salts and hydroxylated derivates

thereof, and several disulfide heteroconjugates (cysteine, homocysteine and glutathione were specifically disclosed). All of these compounds are known in the art.

With regard to the method of administration of the compounds, Applicant has disclosed two preferred methods of administration- oral and parenteral (and intravenous infusion).

With regard to what constitutes an effective amount of formula I compound to be administered Applicant has disclosed that the effective amount to treat accidental radiation exposure can vary between 0.1 mg/kg up to 1000 mg/kg, depending upon the severity of the exposure, and further disclosed that subsequent doses should be administered to maintain effective plasma levels of the formula I compound (or its metabolites).

With regard to the effective amount of formula I compound to be used as prophylaxis, Applicant disclosed the general parameters of what constitutes an effective amount, and then further disclosed a preferred regimen of dosing (disclosing timing as well as amount) and even the most preferred compound and dosing rate and schedule at original page 13 of the specification.

8. Quantity of Experimentation Need to Make or Use the Invention- As noted above, significant instructions and guidance are provided as to dose rate, timing and method of administration, together with a most preferred regimen and compound. A person skilled the art of medicinal chemistry (for this is the proper art field to consider) would have no trouble and would need to perform only routine experiments to determine the proper dosage regimen, as dictated by the condition of the patient.

In conclusion, all claims of the subject patent application are novel, and no *prima facie* case of obviousness has been established based on The Lancet or Van den Broeke references.

Further, the written description is adequate and enabling under 35 USC 112, as the Examiner had concluded in three prior Office Actions.

Favorable reconsideration for claims 1-16 is respectfully solicited, and a Notice of Allowance is respectfully solicited.

Respectfully submitted,

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M is hydrogen or an alkali metal ion; or

a pharmaceutically acceptable salt thereof.

Given the formula I structure, compounds that are contemplated to be effective in the treatment method of this invention include mesna, dimesna (thiethonate), the phosphonate salts of mesna or thiethonate, certain hydroxylated derivatives thereof, and disulfide heteroconjugates of sulfur-containing amino acids, such as cysteine, homocysteine, glutathione and others.

Effective amounts of the formula I compounds to be administered according to the method of this invention vary, and depend of the severity of the patient's exposure to radiation, the route of administration, and other factors. Ranges of preferred dosage amounts and schedules, as well as preferred methods of administration are set forth below.

Accordingly, it is an object of this invention to provide for a method of safely and effectively treating a patient for exposure to radiation.

Other objects will become apparent upon a reading of the following description.

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